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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/297,092	05/18/99	PAULISTA M	P564-9010

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EXAMINER	
STROUP, C	
ART UNIT	**PAPER NUMBER**
1633	8

DATE MAILED: 04/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/297,092	Paulista et al
Examiner	**Group Art Unit**
Stroup, Carrie	1633

☒ Responsive to communication(s) filed on *Feb 9, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *14-27* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *14-27* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's amendment filed 2/9/00 (Paper No. 8) has been entered. Claims 1-13 have been cancelled. Claims 14-27 are currently pending in the present application.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claimed invention is to an implant comprising a protein fragment of the TGF-β superfamily, or DNA encoding thereof (claim 15); and a portion of a mature part of the protein sequence of SEQ ID NO: 1 which has essentially the same cartilage-inducing and/or bone-inducing activity as the mature part, a protein sequence which corresponds with said portion of protein while differing due to the origin of the protein from other vertebrates but having essentially the same function, and a fusion protein, heterodimer, or a protein containing a dimeric mature protein of any of the above (claim 16). The specification discloses that SEQ ID NO: 1 is the complete amino acid sequence of the precursor protein of the human TGF-β protein MP52 (page 21, para 3), and 'that the term "protein of the TGF-β superfamily with a cartilage-inducing and/or bone-inducing activity" denotes a protein which in its mature part contains

the characteristic 7 conserved cysteines, which includes members of the TGF-β, activin, BMP and GDF family and fragments thereof with basically the same activity' (pg 9, para 4). The specification also discloses regarding the fusion proteins that "The corresponding nucleotide and protein sequences are also found in the above-mentioned citations to the disclosure of which reference is herewith made." (Pg 10, para. 2), wherein it is noted that the specification incorporates by reference a list of review articles on members of the TGF-β superfamily (pg 1, para. 2-pg 4, para. 1). The specification does not indicate what distinguishing feature, other than cartilage and bone-inducing ability, are shared by members of this genus of fragments, portions of proteins, and heterodimers. Thus, the scope of the claims include numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted, yet the specification does not provide guidance as to specific changes to make. Structural features that could distinguish compounds with implants in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, such as which specific protein domains confer cartilage and bone-inducing ability, and because the genus is highly variant, the ability to induce cartilage or bone growth is insufficient to describe the genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Additionally, it is not widely known in the art, nor disclosed in the specification directly or by incorporation by reference of the known existence of MP52, SEQ ID NO: 1, in other species other than humans (claim 16c). Thus, applicant was not in possession of the claimed genus.

3. Claims 14-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an implant material comprising a bioactive material composed of calcium phosphate and at least one

cartilage-inducing and/or bone inducing protein or DNA encoding thereof of the TGF- superfamily and methods of making and using such, does not reasonably provide enablement for an implant material comprising a bioactive matrix material composed of calcium phosphate and at least one cartilage-inducing and/or bone inducing protein or DNA encoding thereof, such as a protein fragment of the TGF-β superfamily, a portion of a mature part of SEQ ID NO: 1, a protein sequence corresponding to SEQ ID NO: 1 but of a different species, or a fusion protein or heterodimer containing a portion of the TGF-β superfamily, and the process of making and using such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses by incorporation by reference members of the TGF-β superfamily (pg 1, para. 2-pg 4, para. 1), but is does not disclose fragments, portions, or heterodimers of said members, or non-human homologues to SEQ ID NO: 1, which have demonstrated the ability to induce cartilage and/or bone growth. Neither is it widely known in the art which specific domains and sequences of the members of the TGF-β superfamily possesses such properties. Therefore, the lack of guidance on the coding sequence of specific fragments, portions, or heterodimers, or non-human homologues to SEQ ID NO: 1, would have required a tremendous amount of experimenation by the skilled artisan to ascertain said sequences such that their incorporation into a matrix would result in any cartilage or bone induction in vivo.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been

obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 14-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urist et al (US Patent 4,596,574) in view of Oppermann et al (WO 91/05802) and Yan et al (1995).

Applicant's claimed invention is to a bioactive implant material, and a pharmaceutical composition, comprising a bioactive matrix material composed of a calcium phosphate, such as crystallographically phase-pure alpha or beta tricalcium phosphate ceramic with interconnecting microporosity of 20-60% of its volume, 10-40μm particle size, and causing no giant cell or connective tissue infiltration into the implant material, and further comprising at least one cartilage-inducing and/or bone-inducing protein or DNA encoding therefor, such asTGF beta superfamily protein or a mature protein encoding SEQ ID NO: 1 which is released as the ceramic degrades over time, may be in an injectable suspension. The claimed invention also includes a process of making and using said implant wherein the osteoinductive protein is applied to matrix with appropriate solvent mixtures in such a way that a homogeneous distribution of said protein in the microporous structure is achieved and is conducted through removal of the solvent via freeze drying; and the use of the implant or pharmaceutical composition for the treatment of bone defects.

Urist, MR teaches the use of a biodegradable porous beta tricalcium phosphate ceramic matrix with bone morphogenetic protein (BMP) (col 2, lines 35-44) for the slow release of said protein for the purpose of inducing new bone growth (abstract). Urist, MR also teaches a method of making said matrix with BMP by contacting the porous ceramic with a liquid containing the BMP, then evaporating the solvent through sublimation or freeze drying while entrapping the BMP within the pores of the ceramic (col 3, lines 45-65, & claims 17-18), and leaving the composition in a liquid, hence injectable form which may be shaped as desired (col 4, lines 13-15). Urist also discloses the use of said matrix for the repair of bone in extraskeletal and intraskeletal sites (col 4, lines 40-45). Urist et al do not disclose the use of ethanol precipitation or bioactive materials.

Oppermann et al teach a collagen matrix and a method of making such wherein a recombinantly produced osteogeneic homodimeric proteins such as OP1-16V (claim 2) is interspersed within the pores of the matrix via ethanol precipitation (pg 51, para 1) and released from the matrix in a sustained release manner (pg 44, para 4). Said matrix is utilized for the repair of orthopedic, periodontal, and reconstructive procedures (pg 44, para 4).

Yan et al disclose that materials comprising predominantly tricalcium phosphate are bioactive, as demonstrated by their ability to induce bone growth *in vivo*. Yan et al also diclose that said materials are also biocompatible due to their demonstrated low toxicity and low inflammatory response *in vivo* (abstract).

Fujino et al teach the identification of MP52, a which has 100% identity to SEQ ID NO: 1. (Accession W11900), and discloses its use in bone induction.

Hoetten et al teach the identification of transforming growth factor differentiation 5, a cartilage-derived morphogenetic protein which has 100% identity to SEQ ID NO: 1 (Accession JC2347), and proposes its use in cartilage growth induction.

In light of Urist, Oppermann, Yan, Hoetten and Fujino et al it would have been obvious to one of ordinary skill in the art to combine the tricalcium phosphate ceramic implant of Urist et al with a TGF-β superfamily protein, such as MP-52 (SEQ ID NO: 1), and to make said implant utilizing ethanol precipitation or sublimation. One would have been motivated to do this to deliver a growth factor in a time release controlled manner to a tissue in need of repair or regeneration of cartilage (Hoetten et al, abstract) or bone (Fujino et al, abstract); and because the use of ethanol precipitation or freeze drying were known standards in the art of forming a matrix with a therapeutic protein (Urist, col 3, lines 45-65, & Oppermann et al, pg 51, para 1) . There would have been a reasonable expectation of success because of Oppermann's et al and Urist's demonstration of the ability to utilize modified growth factors seeded within the pores of a biodegradable matrix to regenerate bone (full patents), while Hoetten teaches that SEQ ID NO: 1 is a growth factor to regenerate cartilage. Therefore, one of ordinary skill in the art would have known that substitution of

SEQ ID NO:1 would have resulted in cartilage and/or regrowth enhancement. (It is noted that the pore size and microporosity measured as a percent volume is a result effective variable which one of ordinary skill could modify via methods of solvent precipitation, sintering, and particulate and salt leaching- See Laurencin et al, US Patent 5,866,155, col. 3, line 14-col. 4, line 32). It would also have been obvious to one of ordinary skill in the art to use said implant or composition comprising such to treat a bone or cartilage defect, fracture, or replacement, such as in cosmetic or plastic surgery or in periodontosis. One would have been motivated to use the claimed invention for such because it was routine in the art of tissue engineering at the time of the invention to utilize matrices, such as calcium phosphate or collagen, with growth factors for implantation in vivo to promote the regrowth and differentiation of tissue (Oppermann et al, pg 44, para 4; Urist, col 4, lines 40-45).

No claim is currently allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-0294.

Carrie Stroup

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